PROPHYLACTIC MASTECTOMIES: OCCULT HISTOLOGY AND FISCAL IMPACTS OF SURVEILLANCE VS. SURGERY

Abstract

Introduction

During the last decade, our institution saw a 260% increase in bilateral breast reconstruction cases, consistent with national trends. We reported a drop in average age of prophylactic mastectomy from 57 to 51 years. There is limited data on the likelihood of histological abnormalities in this population. This study measures the prevalence of occult histological findings in prophylactic mastectomy patients. Given the current healthcare reform climate, we estimate the lifetime cost implications of prophylactic mastectomy with immediate reconstruction vs. surveillance.

Methods

A retrospective database of breast reconstructions at the Massachusetts General Hospital was searched from 2004 to 2011 for prophylactic mastectomy patients. Breasts with prior biopsy-proven LCIS, DCIS, or cancer were excluded. Patient demographics, risk factors, and pathology reports were collected. Lifetime treatment reimbursements were estimated with 2013 rates from the Center for Medicare and Medicaid Services using Medicare billing codes. Reimbursements were estimated for 45-year-old patients undergoing contralateral prophylactic mastectomy and 40-year-old patients undergoing bilateral prophylactic mastectomies, and then were compared to women opting for surveillance. Conversion rates to cancer in these patients were used to estimate the percentage patients in the surveillance groups that would need therapeutic mastectomy. Sensitivity analyses were done to test the robustness of the models.

Results

495 prophylactic mastectomy specimens were identified, of which 2.0% had invasive cancer, 4.4% had ductal carcinoma in situ (DCIS), and 10.9% had lobular carcinoma in situ (LCIS) as the highest-risk lesion. Only age group was predictive of finding DCIS or cancer (P=0.02). The likelihood of finding LCIS, DCIS, or cancer increased with age group (P<0.001) and decreased with prior bilateral salpingo-oophorectomy (BSO)(P=0.02). In almost all scenarios, lifetime reimbursements were lower for pursuing either contralateral or bilateral prophylactic mastectomy, with immediate single-stage implant, expander, or abdominal perforator free flap (DIEP) reconstruction, as compared to surveillance.

Conclusions

Prophylactic mastectomy patients have a significant rate of occult histological findings, increasing with age group and decreasing with prior BSO. Lifetime cost estimates suggest a cost-saving role in bilateral and contralateral prophylactic mastectomies. Ultimately, such a critical decision needs to be made individually, but should not be hindered by cost concerns. This study addresses a gap in knowledge with broad interest, contributing evidence of oncologic risk and cost to help guide decision-making in prophylactic mastectomy.

Table of Contents

Glossary……...5

Introduction…….6

Methods……..11

Results……16

Discussion……..19

Summary……27

References……..28

Tables and Figures…….37

Glossary

ASC: ambulatory surgery center

BMI: body mass index

BPM: bilateral prophylactic mastectomy

BSO: bilateral salpingo-oophorectomy

CPM: contralateral prophylactic mastectomy

CPT: current procedural terminology

DCIS: ductal carcinoma in situ

DRG: diagnosis related group

HCPCS: Healthcare Common Procedures Coding System

IPPS: inpatient prospective payment system

LCIS: lobular carcinoma in situ

NCCN: National Comprehensive Cancer Network

OPPS: outpatient prospective payment system

PM: prophylactic mastectomy

QALY: quality adjusted life year

Introduction

As observed nationally, our institution has seen a significant increase in the number of prophylactic mastectomy (PM) procedures. Over the last decade, we experienced a 260% increase in bilateral breast reconstructions, particularly due to increased application of PM in high-risk patients.[1] Recent studies have also shown that the number of women opting for contralateral prophylactic mastectomy (CPM) is increasing among patients with unilateral breast cancer.[2] With early studies showing evidence of at least a 90% drop in risk of breast cancer after bilateral prophylactic mastectomy (BPM), it is easy to understand why that procedure has become more widespread as well.[3] Some studies have even estimated a survival advantage after the pursuit of PM.[4]

Among the subset of high-risk patients are BRCA mutation carriers, who have a significant family history of breast or ovarian cancer, and patients with diagnosed cancer in one breast who choose to undergo CPM.[5] Moreover, patients are also pursuing surgery at a younger age, on average 6 years younger at MGH. BRCA gene status is gradually getting more attention in the lay press and PMs have become a common topic of debate. Women nationwide are increasingly considering risk-reducing mastectomies and reconstructions, and are trying to better determine what risks they face. BRCA testing and counseling in itself has been shown to increase the rate of women opting for bilateral mastectomy by more than 9 times.[6] Concomitant with these trends, more women are opting for nipple-sparing mastectomies (NSM) and single-stage, immediate implant reconstruction whenever possible.[7,8] Therefore, more data are necessary for women to make informed decisions regarding their options, and for physicians and policy-makers to understand the implications of PMs and reconstructions on a national level.

A recent study by Rai et al. analyzed 301 CPMs, and showed a 2.7% rate of occult cancer in the contralateral breast.[9] A similar study investigated the rate of occult histology in subareolar

biopsies of 80 patients undergoing NSMs to assess the safety of leaving the nipple intact, but did not report the histology of the actual mastectomy specimen overall.[10] Smaller studies evaluating for malignancy in 30 BRCA positive patients undergoing PMs found no cancers, but conclusions were limited due to sample size.[11] There have been more studies published in the literature, which indirectly report on the histological findings of PM specimens, but have not discussed risk factors or categorized the findings by patient demographics. Zhou et al. completed a meta-analysis of 1343 patients, and among their findings reported a 1.6% chance of invasive cancer and a 3.3% rate of DCIS.[12-16] Burger and colleagues reported a 1.2% chance of invasive cancer and a 3.6% chance of LCIS among 83 PM specimens, but also only as a secondary outcome, and with no patient breakdown.[17] Evans measured a 3.7% rate of invasive cancer or DCIS.[18] One study of 107 patients looked for predictive factors of occult histology in CPM specimens, but found none.[19] There is a need to understand the risk factors that lead to occult histological findings, especially with the continually increasing demand for PMs. Further, given the prevalence of genetic screening and the awareness surrounding the diagnosis of BRCA1/2 mutation carriers, we need a better understanding of the genetics' role in the timing and appropriateness of PM.

Genetic screening and BRCA diagnoses have only been around since the 1990's, with their use and impact on women's proactive choices to pursue PMs only more recently becoming widespread. There are even less data on the fiscal impacts the treatment options we choose have on lifetime costs of treatment, specifically for breast cancer.[20] Since 2004, with the advent of immediate breast reconstruction options becoming more popular, mastectomies have also become more popular, particularly PMs.[21] In the last decade, nipple-sparing mastectomies and direct-to-implant (also known as "single-stage implant") immediate reconstructions have also become increasingly popular, adding to the reconstructive repertoire, and gaining in use

particularly within the PM patient population. In this study, we estimate the lifetime reimbursements of high-risk women choosing to start with either surveillance of at-risk breasts or proceed to prophylactic mastectomy, and modeling the different possibilities of immediate reconstruction. Moreover, given the dearth of data comparing the lifetime costs of choosing surveillance or prophylactic mastectomy with immediate reconstruction, estimating the economic impacts of these choices are critical to understanding the fiscal implications on a national level. Specifically, it is important understand the influence of both BPMs and CPMs. To date, all but one of the studies that have evaluated the costs of risk reduction focused on BPMs instead of CPMs.

Anderson and colleagues completed a cost-utility analysis comparing different surveillance and preventive strategies in BRCA gene carriers, estimating that the most cost-effective approach was PM with bilateral salpingo-oophorectomy (BSO), increasing in cost-effectiveness the younger the patient was, and costing as little as $100 per quality-adjusted life year (QALY) gained.[22] However, endometrial cancer, pulmonary emboli, and cataracts were the only complications included in the model. The costs of reconstructive options were not included. The standard threshold used to decide whether a treatment is cost-effective is $50,000/QALY, meaning anything below that is considered a worthwhile investment. Therefore, $100/QALY is a bargain. Another study estimated that PM and BSO had a survival advantage, and in the highest-risk patients, also led to QALY gains.[4] According to its estimates, PM was up to an additional $1,277/QALY, still well within range of cost-effectiveness. A follow-up study by Grann estimated that BPM and BSO were both less expensive throughout a patient's life than starting with tamoxifen treatment or regular surveillance, sometimes more than an estimated $40,000 in savings throughout a patient's lifetime.[23] Although the study did estimate a contribution to overall patient survival, its estimates suggested a slight drop in quality of life. Lastly, a

Norwegian study estimated cost savings in pursuing prophylactic BSO and BPM, especially after including the productivity gains and indirect costs associated with long-term gains, as well as an increase in life expectancy based on its model of BPM at age 30 and BSO at 35.[24]

The cost of CPMs has also been estimated, and was also found to be cost-effective in comparison to surveillance. One study evaluated the cost-utility of 45 year old women undergoing CPM in the setting of unilateral breast cancer, comparing it to surveillance, and including the likelihood of recurrences and further treatments.[25] Slightly more expensive than surveillance, CPM led to an increase in QALYs and a cost-effectiveness ratio of $4,869/QALY, again well below the $50,000/QALY threshold. However, this study, just like all of the cost estimates of BPM mentioned previously, did not take into account reconstructive choices made by the patients and the likely complications, revision rates, and follow-up associated with each of those choices. Especially since the passing of the Women's Health and Cancer Right's Act of 1998, which established that insurers must cover the breast reconstructions of women who undergo mastectomy, it is critical to understand not only the impact of mastectomy trends, but also their associated reconstructions.[26]

This study aims to address the question of whether we, both individually and as a society, should continue to increasingly pursue PMs by evaluating two components: histology and lifetime cost. First, what is the rate of occult histological findings in high-risk women pursuing BPMs or CPMs, and are there discernable predictive factors? Second, what are the lifetime financial implications of these findings as more women continue to opt for risk reduction? Given the many reconstructive choices patients have to choose from, the latter question must be answered with an understanding of the impact each reconstructive method has on lifetime treatment costs. We hypothesize that the rate of occult histological findings is greater in the high-risk patient population, possibly highest in BRCA positive patients, given their higher

cumulative lifetime risk of breast cancer. Additionally, the increased initial costs of prophylactic mastectomy may balance with overall savings in breast cancer treatments further in life, leading to overall cost-savings even after factoring in the reconstruction costs. If so, we hope that our findings will guide us to make more informed decisions about the best courses of action.

Methods

Study subjects

This retrospective study is based on patients treated at a tertiary academic medical center between 2004 and 2011. It was reviewed and approved by the Massachusetts General Hospital (MGH) Institutional Review Board. Surgeons involved in the cases were from the Gillette Center for Breast Cancer and the Division of Plastic and Reconstructive Surgery at MGH. A prospectively-maintained database of implant breast reconstructions was used to identify patients undergoing mastectomies on both breasts. No comparable autologous-based reconstruction database was available, so those patients were not included in this study. Inclusion criteria were having a listed indication of prophylactic mastectomy in one or both breasts and having the mastectomy specimens' pathology available in the patient's electronic medical record. Prophylactic mastectomy in this study is defined as mastectomy of a breast that has not had a prior biopsy suggestive of cancer. Patients with prior biopsy of findings of lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), or carcinoma in the breast(s) considered prophylactic were excluded from the study. Preoperative imaging was not necessary for inclusion.

Data retrieval

Using each patient's medical record number, the following variables were collected: age, BMI, history of smoking, radiation, chemotherapy, and bilateral salpingo-oophorectomy (BSO), BRCA status, family history of breast or ovarian cancer, number of breasts treated with prophylactic mastectomy. The most concerning lesion for each prophylactic mastectomy specimen was noted (in order: normal, atypia, LCIS, DCIS, carcinoma). Age group for each

patient was determined by the patient's decade of life (age 20-29, 30-39, 40-49, 50-59, 60-69, 70+).

Statistical analyses

Data were analyzed using STATA 12.1 for Mac (StataCorp, College Station, TX), using p-value < 0.05 as statistically significant. Univariate analyses were conducted with a chi-squared test to determine differences between groups, and Fisher's exact test was used to compare groups with outcome samples too small for chi-squared tests. 2-sided student t-test with equal variance but unequal sample size was used for comparing continuous variables in patient demographics. A final multivariate logistic regression model was used to measure the significance of a change in one variable while adjusting for the effects of the other variables.

Reimbursements

Physician, anesthesia, hospital, and ambulatory surgery center reimbursements were used to estimate the lifetime reimbursements per patient of choosing surveillance or PM. After therapeutic or prophylactic mastectomy, all patients were modeled to receive immediate breast reconstruction, with one of three reconstructive choices: single-stage direct-to-implant, two-stage expander to implant reconstruction, and abdominal perforator free flap reconstruction. These were considered for women considering CPM or BPM. Reimbursements for 12 groups in total were estimated (Table 1). For patients 1a-1f, reimbursements summed were those in addition to the expected reimbursements necessary for the treatment of their already-diagnosed unilateral breast cancers. Physician reimbursements for each procedure were estimated using Medicare's 2013 fee schedules, using Current Procedural Terminology (CPT) and Healthcare Common Procedures Coding System (HCPCS) codes to look up relevant reimbursements.[27] CPT and

HCPCS codes were also used to look up reimbursements for separate supplies, such as acellular dermal matrix (ADM) and implants. The national index reimbursement level was used. Anesthesia reimbursement rates were estimated using base units, time units, and the 2013 conversion factor ($21.92). Reimbursement rate was estimated with the formula: 2013 conversion factor x (base units + time units). Hospital reimbursements were based on the Acute Care Hospital Inpatient Prospective Payment System (IPPS) using relevant Diagnosis Related Group (DRG) codes. Each reimbursement is based on the 2013 Federal Operating Base Payment Rate ($5,348.76), 2013 Federal Capital Base Payment Rate ($425.49), and the DRG Relative Weights for each hospital admission.[28] Each DRG encapsulates a group of hospitalizations expected to have a similar resource use and equal reimbursement.[29] Follow-up procedures that are appropriate to do in an ambulatory surgery center (ASC) were modeled using the Outpatient Prospective Payment System (OPPS) that covers all of the facility costs through a bundled ASC payment rate.[30] Payment rates from January 2013 were used.[31] The billing codes used are listed in Table 2. Given the variability in how radiation therapy and chemotherapy are applied, and how billing is done depends on the treatment and methods of application, the costs of radiation and chemotherapy used were based on prior estimates in the literature.[32] Indirect costs on society and productivity were not included. Terminal costs of health care for patients at the end of life were not estimated.

Models

Decision tree models were built for all groups. For groups choosing surveillance, the probability of each patient developing breast cancer was based on age-dependent probabilities for each patient subtype in the literature.[25,33] Specifically, it was for patients with a prior history of breast cancer undergoing surveillance of the contralateral breast, or BRCA carriers with no

prior history of breast cancer in either breast. Decision trees spanned 30 years at 5-year intervals (Figure 1). Patients opting for PMs were assumed to undergo surgery at the beginning age of their respective models. The National Comprehensive Cancer Network (NCCN) breast cancer guidelines were used to model surveillance, preoperative testing, treatments, and post-operative follow-up.[34-36] For situations without established guidelines, the standard of care at MGH was used. Modeling of operative revisions, nipple-areola complex (NAC) reconstruction, and implant exchanges throughout the 30 year period were included (Tables 3a and 3b).[37-40] The costs and frequency of biopsies, imaging when indicated, and further mammographic screening were also considered. Rates of radiation and chemotherapy use for each patient situation were estimated from the patient demographics presented in this study. Estimates for cost of neoadjuvant and adjuvant chemotherapy was assumed to be the same, although the percentage receiving each type differed for each group.

Reimbursements are presented in 2013 U.S. Dollars ($). The Medical Care Services Index, a component of the Consumer Price Index that includes professional health services and hospital services, was used to estimate the yearly growth in reimbursements. Reimbursements were adjusted for inflation.[41] The yearly inflation-adjusted increase in the Medical Care Services Index averaged 1.63% over from 2003-2013, so an estimate of 1.5% was used for baseline models.[42] A 3% discount rate was applied to calculate the present value of reimbursements over 30 years.

Sensitivity analyses

The yearly inflation-adjusted growth in reimbursement rates was varied from 0-3%, given the variability in inflation from year to year. The discount rate was varied from 0-7%, based on the standard set by the Recommendations from the Panel on Cost-Effectiveness in Health and

Medicine.[43] Additionally, another sensitivity analysis was done that simultaneously varied all of the inputs that could significantly lower the price of surveillance vs. PM, in order to fully ascertain the robustness of the models, even in the most stringent of scenarios.

Results

Histology

Patients who underwent a BPM were more likely to be BRCA positive, have a family history, and have a prior BSO. Of note, BRCA positive patients were found to have undergone a BSO more frequently (42% vs. 7%, p-value <0.001) and to have been 2 years younger on average (43.2 vs. 45.2, p-value=0.017). Those who underwent a CPM were more likely to undergo chemotherapy and radiation (Table 4). Overall, 10 (2.0%) of the PM specimens had cancer, 22 (4.4%) had DCIS, 54 (10.9%) had LCIS, and 104 (21.0%) had atypia as the highest risk lesion. In univariate analyses, the likelihood of malignant pathology (DCIS or cancer) per specimen only significantly increased with each decade life in CPM patients (P-value = 0.020), but otherwise was unaffected by any of the measured variables (Table 5). Meanwhile, abnormal pathology (LCIS, DCIS, or cancer) per specimen increased even more significantly with each decade of life (P-value < 0.001), rising from 0% in patients under 30 years old to 37% in patients older than 60 years of age (Figure 2). Abnormal pathology was more likely in specimens of BRCA negative patients (22.2%) than in those of BRCA positive patients (8.9%, P-value = 0.019). Specimens of patients with prior BSOs less frequently had abnormal pathology than those without (7.7% vs. 19.9%, P-value = 0.003). Family history, BMI ≥ 30, smoking history, and chemotherapy did not have statistically significant impacts on the rate of histological findings in univariate analysis. A summary of the abnormal pathology findings is presented in Table 6. A multivariate logistic regression confirmed age group to be independently predictive of malignant pathology in each specimen, while age group and preoperative BSO status were both independent predictors of abnormal pathology when controlling for other variables (Table 7).

Lifetime reimbursements

Among patients with unilateral breast cancer, those who underwent CPM at the time of therapeutic mastectomy added significantly less to the estimated reimbursements than those who chose surveillance. Specifically, among patients who chose implant, expander, and abdominal perforator free flap (DIEP: Deep Inferior Epigastric Perforator) reconstruction after PM, the baseline model estimated lifetime savings of $7,017 (Group 1d – 1a), $7,101 (Group 1e – 1b), and $7,495 (Group 1f – 1c), respectively.

For BRCA positive patients considering BPM, patients choosing BPM usually spent less than those choosing surveillance, except for patients opting for expander-based reconstruction (Group 2b vs. 2e). Specifically, patients opting for prophylactic mastectomies spent $1,231 less if they underwent single-stage implant reconstruction (Group 2d vs. 2a) and $7,391 less if they underwent immediate DIEP reconstruction (Group 2f vs. 2c). However, those opting for expander-based reconstruction after prophylactic mastectomy spent an estimated $109 more than patients choosing surveillance (Group 2e vs. 2b).

Sensitivity analyses

Sensitivity analyses were conducted first by varying inflation-adjusted growth rates from 0-3% and discount rates from 0-7%. Those sensitivity analyses are presented in Table 8a for CPM patients and in Table 8b for BPM patients. Additionally, we also conducted a sensitivity analysis each for CPM and BPM patients by varying the inputs that were most likely to have significant impacts on the lifetime reimbursements of surveillance and prophylactic mastectomies. After changing certain baseline assumptions in Tables 3a and 3b simultaneously, which are detailed under the "sensitivity analysis" columns, CPM was still cost-saving across all three reconstructive choices. Specifically, it would save an estimated $6,875 for single-stage

implant reconstruction, $6,958 for expander reconstruction, and $7,305 for DIEP reconstruction. For BPM, only DIEP reconstruction remained cost-saving at an estimated $5,826 less than surveillance. For single-stage implant and expander-based reconstructions, prophylactic mastectomy would cost $841 and $2,137 more than surveillance, respectively.

Discussion

As the frequency of contralateral and bilateral PMs continue to increase, women are seeking more proactive approaches to risk reduction. There has even been a 50% increase in the rate of BPM for women with LCIS, with 16% of them opting for BPM in 2009.[44] More information was needed regarding the occult histology in these patients' breasts, and an understanding of the trend's impact on lifetime costs of treatment was warranted. This study addressed both. Specifically different from prior studies were the findings of predictive factors of histology, the inclusion of reconstruction costs throughout the patient's lifetime, and including three different reconstruction methods. Our results suggest that this patient population has a significant rate of occult histological findings and that prophylactic mastectomies with immediate reconstructions have a cost-saving role in most scenarios.

The rate of occult histological findings in both CPM and BPM patients was high, as hypothesized given the lifetime incidence of cancer in BRCA positive patients and high-risk patients with a prior history of unilateral breast cancer. We found that 6.5% of the breast specimens had DCIS or cancer, as compared to 0.3-1.0% in studies of reduction mammoplasty specimens.[45-48] Meanwhile, the rate increased to 17.4% when including LCIS, compared to 0.4-1.3% in reduction mammoplasty specimens of the same studies, representing at least a 13-fold increased risk in our sample. The results are in line with our original histological hypothesis. Our CPM results are similar to a smaller study of 301 patients, with malignant pathology in 4.3% of specimens, slightly lower than our 6.9%.[9] Given our larger sample size, the actual prevalence may be closer to our 6.9%. A study with 239 patients found 7.9% had abnormal pathology in contralateral specimens, significantly lower than our 19.4%, and possibly indicative of slightly higher risk patients in our sample.[49] Particularly surprising was the 0.586 odds ratio of abnormal pathology in specimens of BRCA positive patients even after adjusting for other variables. The

p-value of 0.122 suggests that perhaps a larger sample size would find statistical significance, but our data are not sufficient to suggest a difference in the prevalence of findings in BRCA positive patients. BRCA patients' abnormal pathology prevalence in smaller studies has ranged from 3.4% to 10%.[50,51] However, the patients in those studies were younger on average, which may explain their findings' discrepancy with our 12.3%. The findings that prior BSO and younger age reduce abnormal pathology are consistent with previously published data.

The rate of LCIS was important to consider given the 8-10 fold increased risk of cancer in these patients.[52] In addition, the National Cancer Institute recognizes BPM as a treatment option for these patients, and younger women have been shown to more commonly pursue BPM when diagnosed with LCIS.[44,53] Therefore, given the increasing trend of risk-reduction through PM, especially in younger patients, we believe the inclusion of LCIS to be relevant to the debate. Nonetheless, some experts consider BPM too drastic, and instead recommend surveillance with annual mammograms or chemoprevention with tamoxifen, which decreases the risk of cancer in LCIS patients by 56%.[34,54] For that reason, we also analyzed malignant pathology separately.

The models suggest that CPMs and BPMs often have a cost-saving role when comparing surveillance versus prophylaxis within the same reconstructive choice (single-stage implant, expander, or DIEP). The only exception is BPM with expander-based reconstruction, which was only $109 more expensive. For unilateral breast cancer patients, opting for CPM at the time of therapeutic mastectomy was cost-saving in all scenarios. The savings occur because most of the necessary testing, office visits, and hospitalizations, and follow-up costs would be done at the same time as treatment for the cancerous breast. Moreover, many of the treatment and follow-up costs, such as screening MRI's, have reimbursements that are barely affected by whether the service is unilateral or bilateral, meaning many of the reimbursements would have been rewarded similarly even if only the therapeutic mastectomy had been done. Opting for surveillance will

potentially require additional hospitalizations, anesthesia, and operations at times that would not overlap with the therapeutic mastectomy, and thus add significant costs to the original expenses of treating unilateral breast cancer.

The models for patients considering BPM were closer in lifetime reimbursement costs. The total inflation-adjusted reimbursements of choosing prophylaxis was $1,231 less than surveillance with implant reconstruction, and $7,391 less for DIEP reconstructions. These estimates include the 3% discount rate over the 30-year period, which helps to capture the real dollar value over the period of time by taking into account the time-value of money. These estimates reinforce the belief that women who desire risk-reducing mastectomies with immediate reconstruction should be covered by insurance and Medicare, because they are estimated to save money in the long run. The up front costs of having all interested women pursue PMs balance out by diminishing the need for future MRI's, mammograms, biopsies, and the higher costs of treatment of therapeutic mastectomies, especially because more of those women undergo chemotherapy and radiation. Moreover, opting for PM increases the likelihood of being a candidate for NSM, which has been shown to increase patient satisfaction due to improved aesthetic result.[10,40,55] Younger patients after BPM rarely need radiation and chemotherapy, further improving the aesthetic outcomes and diminishing the likelihood of complications.[56] Not all changes are beneficial. For example, although risk-reducing mastectomy and reconstruction leave most women satisfied with their breast sizes, nearly half of them think their reconstructed breasts were too hard.[57] These considerations are equally important for patients to be aware of, as the more informed women are about their options and the more empowered they feel to choose the option they consider most appropriate, the higher the likelihood that they will be satisfied. Our results are consistent with the prior studies that showed incremental cost-effectiveness of prophylactic mastectomy over other preventive strategies.[22] Our estimates go

further by also estimating the cost of reconstructions, both immediately and of future revisions that patients will likely require or desire in their lifetimes.

The strengths of this research should be broken down into the histological analysis and the lifetime reimbursement estimates. To our knowledge, this is the first study of this size to identify predictive factors of occult histology in BRCA women. Additionally, the inclusion of CPM women without BRCA expands the patient population considered and allows us to better compare to other studies who have also studied occult histology in CPM patients. After identifying likely predictive factors through a univariate analysis, the variables were further analyzed in a multivariate analysis, which helped solidify the identification of younger age and prior BSO as predictive factors of a lower likelihood of occult histology. For the estimates of lifetime reimbursements, this is the first study to analyze the impacts of the different reconstructive options on the estimated costs of treating a patient long-term. With immediate reconstructions becoming more popular, the modeling of three immediate reconstruction choices adds to the versatility of this study, assuring physicians that PM can be cost-effective despite of the reconstructive method used, and improving the ability of surgical oncologists and plastic surgeons to make more informed decisions. Moreover, both CPM and BPM patients were modeled.

Sensitivity analyses were completed for both CPM and BPM patients to test the robustness of the models and the lifetime reimbursement estimates. One set of sensitivity analysis was done by varying economic situations by changing the inflation-adjusted growth rate and the discount rate. For these scenarios, which are included in Tables 8a and 8b, although the absolute value estimates of reimbursements changed significantly for each of the scenarios, in a majority of them CPM and BPM continued to be more cost-effective throughout the patients' lifetimes than surveillance. The results of that sensitivity analysis suggest that despite whatever

economic realities the United States faces in the next 30 years, chances are that PMs will continue to be cost-effective. Moreover, we also decided to conduct a sensitivity analysis by varying the inputs that could favorably reduce the cost of surveillance relative to PM. By changing all of those inputs at once, as presented in Tables 3a and 3b, we measured the impact they could have on our lifetime reimbursement estimates. Despite changing all of the variables to a more favorable position for surveillance, the impacts were minimal across all of the models. All of the CPM models remained cost-saving, and only the single-stage implant reconstruction model after BPM became more expensive than surveillance, although only by $841, which is a small difference when spread out over a patient's lifetime. Expander-based reconstruction remained slightly more expensive also after BPM, but also did not change significantly from the original model. These sensitivity analyses suggest that in many scenarios, despite changing assumptions, PMs continue to be cost-effective.

Limitations of the study should also be broken down into histological analysis and reimbursement estimates. One limitation of the histological analysis is that preoperative radiological findings were not evaluated. Some studies have excluded patients with concerning mammogram or MRI findings, but to maximize sample size, we did not require preoperative imaging for inclusion. Some patients could potentially have been excluded with radiological findings, which could make our findings slightly higher than they would be in if all patients were confirmed to be radiologically-negative. In contrast, a small percent of women have neoplastic cells in their nipples, so the higher proportion of NSMs at our institution may lead to an underestimation of the prevalence of occult histology.[8] Additionally, MGH is a referral center for many complex patients. Therefore, the high-risk patients requesting prophylactic mastectomies at MGH may be more likely to have occult histology than the high-risk patients pursuing surgery elsewhere, as those with really high risk may be seeking out more advanced centers, such as

MGH. Yet another histological limitation is that the study size did not have the power to detect differences between BRCA and non-BRCA carriers during multivariate analysis. Finally, this study did not measure the occult histology in patients undergoing autologous breast reconstruction, as an equivalent database was not available. While the occult histological findings are likely similar in that patient population, it is possible that those patients have higher BMI's on average, and slightly different histological findings. Therefore, the findings in our patient population must be extrapolated to those patients with caution.

The modeling of lifetime reimbursements also has its limitations in what is included, how it is coded, variability in reimbursement, and accuracy in literature predictions. As in all models, ours are also a reduced representation of reality, meaning that every reimbursement that is billed in real life is not included in our models. For example, our models do not include the terminal costs at the end of life, the gradual passing away of more patients in the surveillance models than in the PM models, the indirect costs of care (e.g. productivity costs), or the follow up treatment costs incurred after post-operative biopsies diagnose patients with a recurrence of cancer. If surveillance patients were on average to die 10 years earlier, and had similar terminal life costs as PM patients, then their limited life expectancy would potentially incur less costs on the health care system, but with a reduced lifespan. Another limitation surrounds the coding of treatments, which are simplified in our models out of necessity. For example, a patient undergoing a revision after an autologous free flap reconstruction may be undergoing revisions of the breasts or donor site, and may be undergoing everything from liposuction and removal of dog-ears to the placement of expanders after the failure of a free flap. These procedures would all be billed differently, yet given the difficulty in accurately predicting all of those different possibilities throughout different patient populations, simplification of coding for revisions is necessary. Furthermore, these models apply a national index reimbursement rate for Medicare payments, to

keep the applicability as broad as possible, but in reality reimbursement varies by location within Medicare, and even more significantly for private insurers. However, since many insurance companies rely on the standards set by Medicare to establish their own reimbursement patterns, although their reimbursements are typically higher in value, they are likely proportional to the Medicare distributions. Therefore the cost-savings should still be present, although possibly on a higher scale. Similarly, we are measuring reimbursements, as they inform the national impact, but do not necessarily reflect the true resource costs of providing these services.

The final category of limitations is the published literature. The success of the models is largely dependent on the accuracy of the assumptions made based on the plastic surgery literature, including everything from the percent of patients receiving radiation to the percent of patients with implants undergoing revisions or explants every year. Two main examples are the cancer incidence rates by age for contralateral cancer in unilateral breast cancer patients and primary cancer in BRCA positive patients. These rates were used to predict the percentage of patients starting with surveillance that would ultimately require a therapeutic mastectomy. Another limitation of the published literature for making estimates through models is the granularity of data. For example, to make the best possible predictions, one needs studies that can show the difference in reoperations, if any, between unilateral and bilateral breast reconstructions, between radiation effects in patients who have single-stage implant reconstructions, expander-based reconstructions, and autologous reconstructions. Data for all possible scenarios used in our model were not available. For example, we were unable to find useful data on what percentage of patients undergoing sentinel lymph node biopsies ultimately also require an axillary dissection, so we simply modeled it with 10% for most models. For the revisions of unilateral and bilateral procedures, we assumed the revision rate per patient to be the same because we did not find reliable data on the differences between the two, and because

many unilateral patients ultimately undergo symmetrization procedures, so for simplification we assumed the rates to be the same as for patients who underwent bilateral reconstructions. Using the same logic, we made the assumption for modeling purposes that women who underwent CPM would ultimately have revisions at the same time that they needed to for their original breast cancers, and therefore were part of the same procedures and hospitalizations. However, it is reassuring that throughout the sensitivity analyses for all patient groups, most scenarios remained cost-saving for women choosing PM. The cost estimates are also limited to women undergoing immediate breast reconstruction, and therefore may not be applicable to women undergoing delayed breast reconstructions.

Future studies evaluating occult histological findings in this PM patients should further investigate the possibility that BRCA patients may have a lower rate of abnormal pathology as opposed to non-BRCA patients seeking PM. A larger sample size than ours would be needed to evaluate BRCA gene carrier status within a multivariate analysis. For estimating costs, it would be best to reflect on the actual billing patterns over a 15-20 year period for these patients. What did the hospitals and physicians bill? How much money related to breast cancer or prevention was rewarded? Actual data, as opposed to predictions based on literature estimates of revisions, cancer incidence, etc. would provide more useful data, but is still a few years away, as BRCA testing and the immediate reconstructions modeled in this study have not been around long-enough to measure actual costs.

In 2011, there were an estimated 288,130 breast cancer cases in the U.S. If those patients had all undergone a CPM, the nationwide lifetime savings would be worth slightly more than $2 billion.[58] Meanwhile, an estimated 1% of the general population has the BRCA mutation.[59] If an estimated 150 million women live in the U.S., about 1.5 million are BRCA mutation carriers, with about 20,000 women per year turning 40 with a BRCA diagnosis. If all of those patients

underwent BPM with either single-stage implant reconstruction or DIEP reconstruction, the savings per year would be anywhere between $24 million to over $147 million.

Summary

This study lends support for decisions of CPM and BPM as options that are not only appropriate for high-risk patients who want risk-reduction, but are also cost-saving long-term. As costs continue to constrain healthcare delivery, we can rest assured that these procedures are not worsening the cost-burden on our society. Moreover, the significant findings of abnormal pathology clearly suggest that these high-risk patients pursuing PM are at a significantly higher risk of developing cancer than the general population. Nonetheless, this remains a very difficult and personal decision for many women, as it has many physical and psychological implications, and can only be appropriately weighed by each individual patient with the support of her friends, family, and physicians.

References

1. Fitzpatrick, A. M. *et al.* Cost and Outcome Analysis of Breast Reconstruction Paradigm Shift. *Ann Plast Surg* (2013). doi:10.1097/SAP.0b013e318276d979
2. Cemal, Y. *et al.* A paradigm shift in u.s. Breast reconstruction: part 2. The influence of changing mastectomy patterns on reconstructive rate and method. *Plast Reconstr Surg* **131,** 320e–6e (2013).
3. Hartmann, L. C. *et al.* Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N. Engl. J. Med.* **340,** 77–84 (1999).
4. Grann, V. R., Panageas, K. S., Whang, W., Antman, K. H. & Neugut, A. I. Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. *J. Clin. Oncol.* **16,** 979–985 (1998).
5. Tuttle, T. M. *et al.* Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. *J. Clin. Oncol.* **27,** 1362–1367 (2009).
6. Murphy, R. X., Adkinson, J. M., Namey, T., Eid, S. & Bleznak, A. Surgical and financial implications of genetic counseling and requests for concurrent prophylactic mastectomy. *Ann Plast Surg* **64,** 684–687 (2010).
7. Colwell, A. S. *et al.* Retrospective review of 331 consecutive immediate single-stage implant reconstructions with acellular dermal matrix: indications, complications, trends, and costs. *Plast Reconstr Surg* **128,** 1170–1178 (2011).
8. Colwell, A. S., Gadd, M., Smith, B. L. & Austen, W. G. An inferolateral approach to nipple-sparing mastectomy: optimizing mastectomy and reconstruction. *Ann Plast Surg* **65,** 140–143 (2010).
9. Rai, S. S. *et al.* Contralateral prophylactic mastectomy. *Ann Plast Surg* **67,** 215–219 (2011).

10. Spear, S. L. *et al.* Nipple-sparing mastectomy for prophylactic and therapeutic indications. *Plast Reconstr Surg* **128,** 1005–1014 (2011).

11. Wickman, M., Sandelin, K. & Arver, B. Technical aspects and outcome after prophylactic mastectomy and immediate breast reconstruction in 30 consecutive high-risk patients. *Plast Reconstr Surg* **111,** 1069–1077 (2003).

12. Zhou, W.-B., Liu, X.-A., Dai, J.-C. & Wang, S. Meta-analysis of sentinel lymph node biopsy at the time of prophylactic mastectomy of the breast. *Can J Surg* **54,** 300–306 (2011).

13. Soran, A. *et al.* Is Routine Sentinel Lymph Node Biopsy Indicated in Women Undergoing Contralateral Prophylactic Mastectomy? Magee-Womens Hospital Experience. *Ann. Surg. Oncol.* **14,** 646–651 (2006).

14. Boughey, J. C. *et al.* Contralateral prophylactic mastectomy is associated with a survival advantage in high-risk women with a personal history of breast cancer. *Ann. Surg. Oncol.* **17,** 2702–2709 (2010).

15. McLaughlin, S. A., Stempel, M., Morris, E. A., Liberman, L. & King, T. A. Can magnetic resonance imaging be used to select patients for sentinel lymph node biopsy in prophylactic mastectomy? *Cancer* **112,** 1214–1221 (2008).

16. Black, D. *et al.* Detecting Occult Malignancy in Prophylactic Mastectomy: Preoperative MRI Versus Sentinel Lymph Node Biopsy. *Ann. Surg. Oncol.* **14,** 2477–2484 (2007).

17. Burger, A. *et al.* Sentinel lymph node biopsy for risk-reducing mastectomy. *Breast J* **19,** 529–532 (2013).

18. Evans, D. G. R. *et al.* Risk reducing mastectomy: outcomes in 10 European centres. *J. Med. Genet.* **46,** 254–258 (2009).

19. Barry, P. N. *et al.* Contralateral prophylactic mastectomy: clinical and pathological

features from a prospective database. *Am. J. Med. Sci.* **344,** 452–456 (2012).

20. Ziolkowski, N. I., Voineskos, S. H., Ignacy, T. A. & Thoma, A. Systematic Review of Economic Evaluations in Plastic Surgery. *Plast Reconstr Surg* (2013). doi:10.1097/PRS.0b013e318290f8f8

21. Dragun, A. E. *et al.* Increasing Use of Elective Mastectomy and Contralateral Prophylactic Surgery Among Breast Conservation Candidates: A 14-year Report From a Comprehensive Cancer Center. *Am J Clin Oncol* (2012). doi:10.1097/COC.0b013e318248da47

22. Anderson, K. *et al.* Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. *Ann. Intern. Med.* **144,** 397–406 (2006).

23. Grann, V. R. *et al.* Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. *Breast Cancer Res. Treat.* **125,** 837–847 (2011).

24. Norum, J. *et al.* Prophylactic bilateral salpingo-oophorectomy (PBSO) with or without prophylactic bilateral mastectomy (PBM) or no intervention in BRCA1 mutation carriers: a cost-effectiveness analysis. *Eur. J. Cancer* **44,** 963–971 (2008).

25. Zendejas, B. *et al.* Cost-effectiveness of contralateral prophylactic mastectomy versus routine surveillance in patients with unilateral breast cancer. *J. Clin. Oncol.* **29,** 2993–3000 (2011).

26. *Women's Health and Cancer Rights Act*. (American Cancer Society). at <http://www.cms.hhs.gov/HealthInsReformforConsume/06_TheWomen’sHealthandCancerRightsAct.asp July 2, 2008>

27. *Physician Fee Schedule Search*. (Centers for Medicare & Medicaid Services). at <http://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx>

28. *Acute Care Hospital Inpatient Prospective Payment System*. (Department of Health and Human Services, 2013). at <http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/downloads/AcutePaymtSysfctsht.pdf>

29. *Acute Inpatient PPS*. (Centers for Medicare & Medicaid Services). at <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/index.html>

30. *Ambulatory Surgical Center Fee Schedule*. (Department of Health and Human Services, 2013). at <https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/downloads/AmbSurgCtrFeepymtfctsht508-09.pdf>

31. *Addenda Updates*. (Centers for Medicare & Medicaid Services). at <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ASCPayment/11_Addenda_Updates.html>

32. Barron, J. J., Quimbo, R., Nikam, P. T. & Amonkar, M. M. Assessing the economic burden of breast cancer in a US managed care population. *Breast Cancer Res. Treat.* **109,** 367–377 (2008).

33. Lowry, K. P. *et al.* Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. *Cancer* **118,** 2021–2030 (2012).

34. Bevers, T. B. *et al. Breast Cancer Risk Reduction*. (National Comprehensive Cancer Network, 2013).

35. Bevers, T. B. *et al. Breast Cancer Screening and Diagnosis*. (National Comprehensive Cancer Network, 2013).

36. Theriault, R. L. *et al. Breast Cancer*. (National Comprehensive Cancer Network, 2013).

37. Vega, S. *et al.* 500 Consecutive patients with free TRAM flap breast reconstruction: a single surgeon's experience. *Plast Reconstr Surg* **122,** 329–339 (2008).

38. Mlodinow, A. S. *et al.* Predictors of Readmission After Breast Reconstruction: A Multi-institutional Analysis of 5012 Patients. *Ann Plast Surg* **71,** 335–341 (2013).

39. Man, L.-X., Selber, J. C. & Serletti, J. M. Abdominal wall following free TRAM or DIEP flap reconstruction: a meta-analysis and critical review. *Plast Reconstr Surg* **124,** 752–764 (2009).

40. Mallon, P. *et al.* The Role of Nipple-Sparing Mastectomy in Breast Cancer. *Plast Reconstr Surg* **131,** 969–984 (2013).

41. *CPI Inflation Calculator*. (Bureau of Labor Statistics, U.S. Department of Labor). at <http://www.bls.gov/data/inflation_calculator.htm>

42. *Consumer Price Index*. (Bureau of Labor Statistics). at <http://www.bls.gov/cpi/cpi_dr.htm#2013>

43. Weinstein, M. C., Siegel, J. E., Gold, M. R., Kamlet, M. S. & Russell, L. B. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. in *JAMA* **276,** 1253–1258 (1996).

44. Portschy, P. R., Marmor, S., Nzara, R., Virnig, B. A. & Tuttle, T. M. Trends in incidence and management of lobular carcinoma in situ: a population-based analysis. *Ann. Surg. Oncol.* **20,** 3240–3246 (2013).

45. Ishag, M. T., Bashinsky, D. Y., Beliaeva, I. V., Niemann, T. H. & Marsh, W. L. Pathologic findings in reduction mammaplasty specimens. *Am J Clin Pathol* **120,** 377–380 (2003).

46. Kakagia, D., Fragia, K., Grekou, A. & Tsoutsos, D. Reduction mammaplasty specimens and occult breast carcinomas. *Eur J Surg Oncol* **31,** 19–21 (2005).

47. Goyal, A. *et al.* Occult breast carcinoma in breast reduction specimens in European women. *Breast Cancer Res. Treat.* **128,** 749–753 (2011).

48. Colwell, A. S., Kukreja, J., Breuing, K. H., Lester, S. & Orgill, D. P. Occult breast carcinoma in reduction mammaplasty specimens: 14-year experience. *Plast Reconstr Surg* **113,** 1984–1988 (2004).

49. Goldflam, K. *et al.* Contralateral prophylactic mastectomy. Predictors of significant histologic findings. *Cancer* **101,** 1977–1986 (2004).

50. Arver, B. *et al.* Bilateral prophylactic mastectomy in Swedish women at high risk of breast cancer: a national survey. *Ann. Surg.* **253,** 1147–1154 (2011).

51. Isern, A. E., Loman, N., Malina, J., Olsson, H. & Ringberg, A. Histopathological findings and follow-up after prophylactic mastectomy and immediate breast reconstruction in 100 women from families with hereditary breast cancer. *Eur J Surg Oncol* **34,** 1148–1154 (2008).

52. Oppong, B. A. & King, T. A. Recommendations for women with lobular carcinoma in situ (LCIS). *Oncology (Williston Park, N.Y.)* **25,** 1051–6– 1058 (2011).

53. *Lobular Carcinoma In Situ*. (National Cancer Institute, 2013). at <http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/page5>

54. Fisher, B. *et al.* Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J. Natl. Cancer Inst.* **97,** 1652–1662 (2005).

55. Wellisch, D. K., Schain, W. S., Noone, R. B. & Little, J. W. The psychological contribution of nipple addition in breast reconstruction. *Plast Reconstr Surg* **80,** 699–704 (1987).

56. Serletti, J. M., Fosnot, J., Nelson, J. A., Disa, J. J. & Bucky, L. P. Breast reconstruction after breast cancer. *Plast Reconstr Surg* **127,** 124e–35e (2011).

57. Brandberg, Y. *et al.* Less correspondence between expectations before and cosmetic

results after risk-reducing mastectomy in women who are mutation carriers: a prospective study. *Eur J Surg Oncol* **38,** 38–43 (2012).

58. Alteri, R., Bandi, P., Brinton, L. & Casares, C. *Breast Cancer*. (American Cancer Society, 2011). at <http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-030975.pdf>

59. Spear, S. L., Carter, M. E. & Schwarz, K. Prophylactic mastectomy: indications, options, and reconstructive alternatives. *Plast Reconstr Surg* **115,** 891–909 (2005).

60. Hickman, D., Davis, E., Meyer, S. & Schechtel, M. Core-Needle Biopsy for Breast Abnormalities. *Agency for Healthcare Research and Quality* at <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=406&pageaction=displayproduct>

61. Kontos, M., Roy, P., Rizos, D., Petrou, A. & Hamed, H. Contralateral relapse after surgery for breast cancer: evaluation of follow-up paradigms. *Int. J. Clin. Pract.* **67,** 1113–1117 (2013).

62. *SEER Cancer Statistics Review 1973-1998*. (National Cancer Institute). at <http://seer.cancer.gov/archive/csr/1973_1998/breast.pdf>

63. Warren Peled, A. *et al.* Outcomes after total skin-sparing mastectomy and immediate reconstruction in 657 breasts. *Ann. Surg. Oncol.* **19,** 3402–3409 (2012).

64. Singh, N. K., Reaven, N. L. & Funk, S. E. Cost comparison of immediate one-stage and tissue-expander breast reconstructions after mastectomy in commercially insured patients. *Manag Care* **22,** 36–43 (2013).

65. Palit, T. K., Miltenburg, D. M. & Brunicardi, F. C. Cost analysis of breast conservation surgery compared with modified radical mastectomy with and without reconstruction. *Am*

J Surg **179,** 441–445 (2000).

66. Berry, T., Brooks, S., Sydow, N., Djohan, R. & Nutter, B. Complication Rates of Radiation on Tissue Expander and Autologous Tissue Breast Reconstruction - Springer. *Annals of surgical …* (2010).

67. Rusby, J. E., Waters, R. A., Nightingale, P. G. & England, D. W. Immediate breast reconstruction after mastectomy: what are the long-term prospects? *Ann R Coll Surg Engl* **92,** 193–197 (2010).

68. Roostaeian, J. *et al.* Immediate Placement of Implants in Breast Reconstruction: Patient Selection and Outcomes. *Plast Reconstr Surg* **127,** 1407–1416 (2011).

69. *FDA update on the safety of silicone gel-filled breast implants*. (U.S. Food and Drug Administration, 2011).

70. Damen, T. H. C., Mureau, M. A. M., Timman, R., Rakhorst, H. A. & Hofer, S. O. P. The pleasing end result after DIEP flap breast reconstruction: a review of additional operations. *J Plast Reconstr Aesthet Surg* **62,** 71–76 (2009).

71. Hanwright, P. J. *et al.* The differential effect of BMI on prosthetic versus autogenous breast reconstruction: a multivariate analysis of 12,986 patients. *Breast* **22,** 938–945 (2013).

72. Hofer, S. O. P., Damen, T. H. C., Mureau, M. A. M., Rakhorst, H. A. & Roche, N. A. A critical review of perioperative complications in 175 free deep inferior epigastric perforator flap breast reconstructions. *Ann Plast Surg* **59,** 137–142 (2007).

73. Guerra, A. B. *et al.* Bilateral breast reconstruction with the deep inferior epigastric perforator (DIEP) flap: an experience with 280 flaps. *Ann Plast Surg* **52,** 246–252 (2004).

74. *Silicone Gel-Filled Breast Implants*. (U.S. Food and Drug Administration). at <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsth

etics/BreastImplants/ucm063871.htm>

75. Damen, T. H. C. *et al.* Medium-term cost analysis of breast reconstructions in a single Dutch centre: a comparison of implants, implants preceded by tissue expansion, LD transpositions and DIEP flaps. *J Plast Reconstr Aesthet Surg* **64,** 1043–1053 (2011).

76. Enajat, M. *et al.* Aesthetic refinements and reoperative procedures following 370 consecutive DIEP and SIEA flap breast reconstructions: important considerations for patient consent. *Aesthetic Plast Surg* **34,** 306–312 (2010).

Tables and Figures

Table 1

Group designations	
Unilateral breast cancer patients considering CPM	
1a	Surveillance, implant reconstruction
1b	Surveillance, expander reconstruction
1c	Surveillance, DIEP reconstruction
1d	Prophylaxis, implant reconstruction
1e	Prophylaxis, expander reconstruction
1f	Prophylaxis, DIEP reconstruction
BRCA patients considering BPM	
2a	Surveillance, implant reconstruction
2b	Surveillance, expander reconstruction
2c	Surveillance, DIEP reconstruction
2d	Prophylaxis, implant reconstruction
2e	Prophylaxis, expander reconstruction
2f	Prophylaxis, DIEP reconstruction
Note: Surveillance groups list the type of reconstruction that the patients requiring therapeutic mastectomies would ultimately have.	

Table 2

Billing codes used for cost modeling	
Surveillance and Follow-up	**CPT/HCPCS Code**
Office visit	99214
Computer aided detection with physician review; diagnostic	77051
computer aided detection with physician review of mammogram	77052
Mammography, unilateral	77055
mammography, bilateral	77056
screening mammography, bilateral, 2 view film study of each breast	77057
unilateral breast MRI	77058
bilateral breast MRI	77059
Work-Up	**CPT/HCPCS Code**
Breast biopsy, needle core, using imaging guidance	19102
Breast biopsy, automated vacuum assisted device, with imaging guidance	19103
placement of percutaneous localization clip	19295
MRI guidance for needle placement, radiological supervision and interpretation	77021
Mammographic guidance for needle placement, radiological supervision and interpretation	77032
Level IV- surgical pathology, gross and microscopic exam (breast biopsy)	88305
Level V-surgical pathology exam (mastectomy)	88307
Level VI-surgical pathology exam (breast mastectomy with regional nodes)	88309
Immunohistochemistry (for each antibody)	88342
Comprehensive metabolic panel	80053
CBC, automated, and differential WBC count	85025
Imaging	**CPT/HCPCS Code**
Chest CT	71260
Abdominal/pelvic CT	74177
Bone scan (tomographic SPECT)	78320
Surgery	**CPT/HCPCS Code**
Alloderm unilateral	15777
Mastectomy	19304
Immediate insertion of breast prosthesis in reconstruction	19340
Delayed insertion of prosthesis in breast reconstruction	19342
Nipple reconstruction	19350
Breast reconstruction with TE, including subsequent expansion	19357
Breast reconstruction with free flap	19364
Revision of reconstructed breast	19380

Lymphangiography for node identification	38792
Biopsy or excision of nodes	38525
Axillary node dissection	38745
Implant	L8600
Replacement of expander with implant	11970
Areolar tattoo	11922
Anesthesia	**CPT/HCPCS Code**
Anesthesia for procedures on anterior trunk, not otherwise specified	00400
Anesthesia for breast reconstruction	00402
Anesthesia for mastectomy	00404
Anesthesia for mastectomy with node dissection	00406
Hospitalizations	**DRG Code**
Other breast procedures without major complications	581
Mastectomy with complications	582
Mastectomy without complications	583

Table 3a

Outline of cost model for patients with unilateral cancer Starting age: 45 years Modeling intervals: 5 years Only reimbursements above expected treatment for unilateral breast cancer included			
Group 1: Contralateral surveillance after unilateral mastectomy	**Baseline**	**Sensitivity Analysis**	**Reference**
Before Cancer Diagnosis			
Additional breast exams per year	1		36
Number of biopsies per cancer diagnosis	4		60
Annual percent of patients who develop CBC	0.24%		61
Additional annual mammograms	0		35
Additional screening MRI every two years (other breast undergoing implant rupture screening in between)			
After Cancer Diagnosis			
Preoperative office visits	2		
Diagnostic mammogram, basic laboratory tests			
% of patients at stage III on diagnosis: chest CT, abdominal CT, bone scan	7.40%	5%	62
Neoadjuvant Chemotherapy: % of patients receiving it	59%	40%	MGH, 63
Neoadjuvant chemotherapy: cost per patient receiving it	$6,444	$3,000	25,32
Hopsital admission for skin-sparing contralateral mastectomy			
Lymphangiography with SLNB: % of patients receiving it	100%		MGH
Axillary dissection for positive SLNB or clinically evident nodes: % of patients receiving it	10%	3%	
Immediate reconstruction with implant, expander, or DIEP			
Acellular dermal matrix for single-stage implant reconstructions			
Implant for implant and expander-based reconstructions			
Surgical pathology and immunohistochemistry			
Radiation: % of patients receiving it	38%	10%	MGH, 64
Radiation: cost per patient receiving it	$5,940	$2,000	25,32,65
Adjuvant chemotherapy: % of patients receiving it	18.2%	0%	63
Adjuvant chemotherapy: cost assumed equal to neoadjuvant chemotherapy			
Expander reconstructions: expander to implant exchange at 6 months post-op			
% of patients receiving NAC reconstruction and tattoo	100%		
Long-term follow-up			
Oncologist: additional visits per year for first 5 years	1		36
Additional mammograms per year over those scheduled for prior breast	0		36
Plastic surgeon: additional plastic surgery visits in first year	4		
Plastic surgeon: additional visits per year starting year two	0		
Follow up procedures done in ASC			

Implant and expander reoperations in first 3 years			64,66-68
% of radiated patients undergoing reoperations	45%	20%	
% of non-radiated patients undergoing reoperations	21%	5%	
% of patients with implants or expanders reoperated per year, starting year 4	7.20%		69
DIEP reoperations: radiation does not affect reoperation rate			66
% of patients reoperated in year 1	34.00%	20%	67,70-73
% of patients reoperated in year 2	30%	15%	67
% of patients reoperated in year 3	29%	10%	67
% of patients reoperated in year 4	8%	5%	67
% of patients reoperated in year 5	5%	0%	67
DIEP revision rates after year 5	0%	0%	
Implant rupture screening: additional MRI's over implant rupture screening for prior breast			74
% drop in frequency of biopsies	90%		3
Group 2: Contralateral prophylactic mastectomy at time of unilateral therapeutic mastectomy	**Baseline**	**Sensitivity Analysis**	**Reference**
Preoperative			
Additional preoperative office visits	1		
No additional laboratory tests			
Procedure			
Hospital admission for bilateral skin-sparing mastectomy (already scheduled hospitalization)			
Lymphangiography with SLNB: % of patients receiving it	100%		
Additional axillary dissection for positive SLNB or clinically evident nodes: % of patients receiving it	5%		12
Immediate reconstruction with implant, expander, or DIEP			
Additional acellular dermal matrix for contralateral breast			
Additional implant for implant and expander-based reconstructions			
Surgical pathology			
Immunohistochemistry: % of patients with DCIS or cancer	7%		MGH
Radiation: % of patients receiving it for prophylactic breast	3%		MGH
Radiation: cost per patient receiving it	$5,940	$2,000	25,32,65
Adjuvant chemotherapy: % of patients receiving it for prophylactic breast	3.0%		MGH, 63
Adjuvant chemotherapy: assumed equal to neoadjuvant chemotherapy			
Expander reconstructions: expander to implant exchange at 6 months post-op			
% of patients receiving NAC reconstruction and tattoo	100%		
Long-term follow-up			
Oncologist and plastic surgeon: additional annual visits	0		MGH,
Additional yearly mammograms	0		34
Additional implant rupture screening MRIs	0		
Implant exchanges occur at same time as other breast			
Additional operations	0		

Remaining long-term follow-up assumptions same as group 1			
Note: "Additional" refers to services, tests, or spending additional to what was already scheduled for the unilateral cancer treatment. Any line with no associated reference is an assumption made for modeling. Lines with MGH under the reference column represents data found in our PM specimens or based on a standard of care at MGH. ASC: ambulatory surgery center; CBC: contralateral breast cancer; DIEP: deep inferior epigastric perforator; NAC: nipple-areola complex; SLNB: sentinel lymph node biopsy;			

Table 3b

Outline of cost model for BRCA patients without cancer Starting age: 40 years Modeling intervals: 5 years			
Group 1: Bilateral surveillance	**Baseline**	**Sensitivity Analysis**	**Reference**
Before Cancer Diagnosis Age 25 onward: Breast exam every 6 months, annual screening mammogram and MRI			
Number of biopsies per cancer diagnosis	4		60
5-year conditional probability of cancer-free BRCA patient developing cancer			33
Years 40-45	18.70%		
Years 45-50	12%		
Years 50-55	12%		
Years 55-60	5.30%		
Years 60-65	4%		
Years 65-70	2.70%		
After Cancer Diagnosis			
Preoperative office visits	2		
Diagnostic mammogram, basic laboratory tests			
% of patients at stage III on diagnosis: chest CT, abdominal CT, bone scan	7.40%	5%	62
Neoadjuvant Chemotherapy: % of patients receiving it	59%	40%	MGH, 63
Neoadjuvant chemotherapy: cost per patient receiving it	$6,444	$3,000	25,32
Hopsital admission for skin-sparing bilateral mastectomy			
Lymphangiography with SLNB: % of patients receiving it	100%		MGH
Axillary dissection for positive SLNB or clinically evident nodes: % of patients receiving it	10%	3%	
Immediate reconstruction with implant, expander, or DIEP			
Acellular dermal matrix for single-stage implant reconstructions			
Implant for implant and expander-based reconstructions			
Surgical pathology and immunohistochemistry			
Radiation: % of patients receiving it	38%	10%	MGH, 64
Radiation: cost per patient receiving it	$5,940	$2,000	25,32,65
Adjuvant chemotherapy: % of patients receiving it	18.2%	0%	63
Adjuvant chemotherapy: cost assumed equal to neoadjuvant chemotherapy			
Expander reconstructions: expander to implant exchange at 6 months post-op			
% of patients receiving NAC reconstruction and tattoo	100%		
Long-term follow-up			
Oncologist: 2 annual visits first 5 years, 1 annual visit after			36
Annual mammograms			35

Plastic surgeon: 4 visits in 1st year, annually thereafter			
Follow up procedures done in ASC			
Implant and expander reoperations in first 3 years			64,66-68
% of radiated patients undergoing reoperations	45%	20%	
% of non-radiated patients undergoing reoperations	21%	5%	
% of patients with implants or expanders reoperated per year, starting year 4	7.20%		69
DIEP reoperations: radiation does not affect reoperation rate			66
% of patients reoperated in year 1	34.00%	20%	67,71-73,75,76
% of patients reoperated in year 2	30%	15%	67
% of patients reoperated in year 3	29%	10%	67
% of patients reoperated in year 4	8%	5%	67
% of patients reoperated in year 5	5%	0%	67
DIEP revision rates after year 5	0%	0%	
Implant rupture screening: MRI every 2 years starting year 4			74
% drop in frequency of biopsies	90%		3

Group 2: Bilateral prophylactic mastectomy	**Baseline**	**Sensitivity Analysis**	**Reference**
Preoperative			
Preoperative office visits	2		
Basic laboratory test			
Procedure			
Hospital admission for bilateral prophylactic skin-sparing mastectomy			
Lymphangiography with SLNB: % of patients receiving it	100%		
Axillary dissection for positive SLNB or clinically evident nodes: % of patients receiving it	5%		12
Immediate reconstruction with implant, expander, or DIEP			
Acellular dermal matrix for single-stage implant reconstructions			
Implant for implant and expander-based reconstructions			
Surgical pathology			
Immunohistochemistry: % of patients with DCIS or cancer	7%		MGH
Radiation: % of patients receiving it	3%		MGH, 64
Radiation: cost per patient receiving it	$5,940	$2,000	25,32,65
Adjuvant chemotherapy: % of patients receiving it	3.0%		MGH, 63
Adjuvant chemotherapy: cost assumed equal to neoadjuvant chemotherapy			
Expander reconstructions: expander to implant exchange at 6 months post-op			
% of patients receiving NAC reconstruction and tattoo	100%		
Long-term follow-up			
Oncologist and plastic surgeon: annual visits			MGH
No follow-up yearly mammograms needed			MGH
Remaining long-term follow-up assumptions same as group 1			

Note: Any line with no associated reference is an assumption made for modeling. Lines with MGH under the reference column represents data found in our PM specimens or based on a standard of care at MGH.ASC: ambulatory surgery center; CBC: contralateral breast cancer; DIEP: deep inferior epigastric perforator; NAC: nipple-areola complex; SLNB: sentinel lymph node biopsy;			

Table 4

Patient demographics								
		CPM	**%**	**BPM**	**%**	**Total**	**%**	**P-value**
Patients		377		59		436		
Age	Avg.	44.8		43.4		44.6		0.203
	SD	7.8		7.8		7.8		
	≤ 29	5	1.3%	1	1.7%	6	1.4%	0.043
	30-39	87	23.1%	17	28.8%	104	23.9%	
	40-49	189	50.1%	26	44.1%	215	49.3%	
	50-59	79	21.0%	14	23.7%	93	21.3%	
	≥60	17	4.5%	1	1.7%	18	4.1%	
BRCA	Pos	81	21.5%	49	83.1%	130	29.8%	< 0.001
	Neg	296	78.5%	10	16.9%	306	70.2%	
FH	Yes	276	73.2%	57	96.6%	333	76.4%	< 0.001
	No	101	26.8%	2	3.4%	103	23.6%	
Prior BSO	Yes	44	11.7%	30	50.8%	74	17.0%	< 0.001
	No	333	88.3%	29	49.2%	362	83.0%	
BMI	Avg.	25.2	6.7%	25.1	42.7%	25.2		0.95
	SD	4.8	1.3%	4.5	7.8%	4.7		
	<30	334	88.6%	53	89.8%	387	88.8%	0.7798
	≥30	43	11.4%	6	10.2%	49	11.2%	
Chemo	Yes	224	59.4%	2	3.4%	226	51.8%	< 0.001
	No	153	40.6%	57	96.6%	210	48.2%	
Radiation	Yes	144	38.2%	2	3.4%	146	33.5%	< 0.001
	No	233	61.8%	57	96.6%	290	66.5%	

FH: family history; Prior BSO: bilateral salpingo-oophorectomy before prophylactic mastectomy; BMI: body mass index; ^ 2 prop Ztest

Table 5

Patients or specimens with malignant pathology (DCIS or Invasive Cancer, % with findings)							
		CPM Specimens		BPM Specimens		Total Specimens	
Variable		**Pos**	**%**	**Pos**	**%**	**Pos**	**%**
Age	≤ 29	0	0.0%	0	0.0%	0	0.0%
	30-39	1	1.1%	3	8.8%	4	3.3%
	40-49	13	6.9%	2	3.8%	15	6.2%
	50-59	9	11.4%	1	3.6%	10	9.3%
	≥60	3	17.6%	0	0.0%	3	15.8%
	Total	26	6.9%	6	5.1%	32	6.5%
	p-value	0.020		0.645		0.142	
BRCA	Positive	5	6.2%	4	4.1%	9	5.0%
	Negative	21	7.1%	2	10.0%	23	7.3%
	p-value	0.722		0.268		0.328	
FH	Yes	22	8.0%	6	5.3%	28	7.2%
	No	4	4.0%	0	0.0%	4	3.8%
	p-value	0.250		1.000		0.213	
Prior BSO	Yes	5	11.4%	1	1.7%	6	5.8%
	No	21	6.3%	5	8.6%	26	6.6%
	p-value	0.213		0.111		0.746	
BMI	<30	21	6.3%	6	5.7%	27	6.1%
	≥30	5	11.6%	0	0.0%	5	9.1%
	p-value	0.193		0.398		0.401	
Chemo	Yes	17	7.6%	1	25.0%	18	7.9%
	No	9	5.9%	5	4.4%	14	5.2%
	p-value	0.521		0.191		0.232	

FH: family history; Prior BSO: bilateral salpingo-oophorectomy before prophylactic mastectomy; BMI: body mass index;

Table 6

Patients or specimens with abnormal pathology (LCIS, DCIS, or Invasive Cancer, % with findings)

		CPM Specimens		BPM Specimens		Total Specimens	
Variable		**Pos**	**%**	**Pos**	**%**	**Pos**	**%**
Age	≤ 29	0	0.0%	0	0.0%	0	0.0%
	30-39	3	3.4%	4	11.8%	7	5.8%
	40-49	40	21.2%	4	7.7%	44	18.3%
	50-59	24	30.4%	4	14.3%	28	26.2%
	≥60	6	35.3%	1	50.0%	7	36.8%
	Total	73	19.4%	13	11.0%	86	17.4%
	p-value	< 0.001		0.407		< 0.001	
BRCA	Positive	9	11.1%	7	7.1%	16	8.9%
	Negative	64	21.6%	6	30.0%	70	22.2%
	p-value	0.034		0.003		0.019	
FH	Yes	54	19.6%	13	11.4%	67	17.2%
	No	19	18.8%	0	0.0%	19	18.1%
	p-value	0.87		0.474		0.826	
Prior BSO	Yes	6	13.6%	2	3.3%	8	7.7%
	No	67	20.1%	11	19.0%	78	19.9%
	p-value	0.306		0.007		0.003	
BMI	<30	62	18.6%	12	11.3%	74	16.8%
	≥30	11	25.6%	1	8.3%	12	21.8%
	p-value	0.273		0.754		0.356	
Chemo	Yes	39	17.4%	1	25.0%	40	17.5%
	No	34	22.2%	12	10.5%	46	17.2%
	p-value	0.246		0.363		0.926	

FH: family history; Prior BSO: bilateral salpingo-oophorectomy before prophylactic mastectomy; BMI: body mass index;

Table 7

Multivariate analysis by specimen (n=495)						
	DCIS or cancer			LCIS, DCIS, or cancer		
Variable	**P-Value**	**OR**	**95% CI**	**P-Value**	**OR**	**95% CI**
Age Group	**0.022**	1.686	1.07-2.63	**< 0.001**	2.107	1.54-2.89
BMI ≥ 30	0.317	1.696	0.62-4.78	0.609	1.235	0.55-2.77
Chemo	0.318	1.464	069-3.09	0.697	0.905	0.55-1.50
BRCA Status	0.643	0.798	0.31-2.07	0.122	0.586	0.30-1.15
BSO Status	0.704	0.813	0.28-2.36	**0.015**	0.34	0.14-0.81
Family History	0.201	2.041	0.68-6.10	0.794	1.083	0.59-1.97

Table 8a

Contralateral model sensitivity analysis					
Growth:	**Discount Rates:**	**0%**	**0%**	**3%**	**7%**
0%	**Surveillance**	**Implant**	$13,861	$8,563	$5,028
		Expander	$14,048	$8,678	$5,095
		DIEP	$14,080	$8,691	$5,096
	Prophylaxis	**Implant**	$3,856	$3,770	$3,681
		Expander	$3,919	$3,833	$3,744
		DIEP	$3,506	$3,497	$3,491
1.50%	**Surveillance**	**Implant**	$18,093	**$10,829**	$6,122
		Expander	$18,339	**$10,975**	$6,205
		DIEP	$18,388	**$10,996**	$6,209
	Prophylaxis	**Implant**	$3,906	**$3,812**	$3,714
		Expander	$3,969	**$3,874**	$3,776
		DIEP	$3,512	**$3,501**	$3,493
3%	**Surveillance**	**Implant**	$23,898	$13,861	$7,537
		Expander	$24,222	$14,048	$7,638
		DIEP	$24,295	$14,080	$7,647
	Prophylaxis	**Implant**	$3,962	$3,856	$3,749
		Expander	$4,025	$3,919	$3,811
		DIEP	$3,522	$3,506	$3,495

Note: growth denotes annual raise in prices after adjusting for inflation

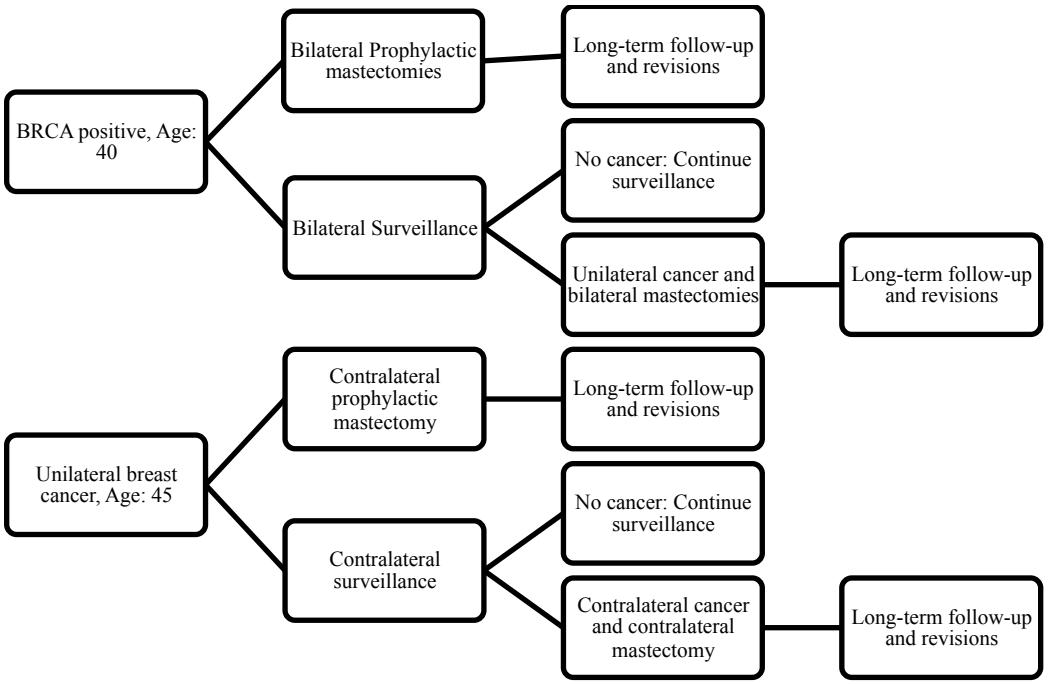
Table 8b

Bilateral model sensitivity analysis					
Growth:	**Discount Rates:**	**0%**	**0%**	**3%**	**7%**
0%	**Surveillance**	**Implant**	$39,903	$25,829	$16,011
		Expander	$41,153	$26,714	$16,611
		DIEP	$37,542	$24,905	$15,819
	Prophylaxis	**Implant**	$35,679	$26,957	$21,171
		Expander	$38,067	$29,345	$23,558
		DIEP	$24,719	$21,698	$19,469
1.50%	**Surveillance**	**Implant**	$50,862	**$31,913**	$19,108
		Expander	$52,376	**$32,961**	$19,802
		DIEP	$47,193	**$30,410**	$18,719
	Prophylaxis	**Implant**	$42,672	**$30,682**	$22,957
		Expander	$45,060	**$33,070**	$25,345
		DIEP	$27,015	**$23,019**	$20,192
3%	**Surveillance**	**Implant**	$65,646	$39,903	$23,028
		Expander	$67,497	$41,153	$23,835
		DIEP	$60,041	$37,542	$22,342
	Prophylaxis	**Implant**	$52,279	$35,679	$25,273
		Expander	$54,667	$38,067	$27,661
		DIEP	$30,076	$24,719	$21,078

Note: growth denotes annual raise in prices after adjusting for inflation

Figure 1

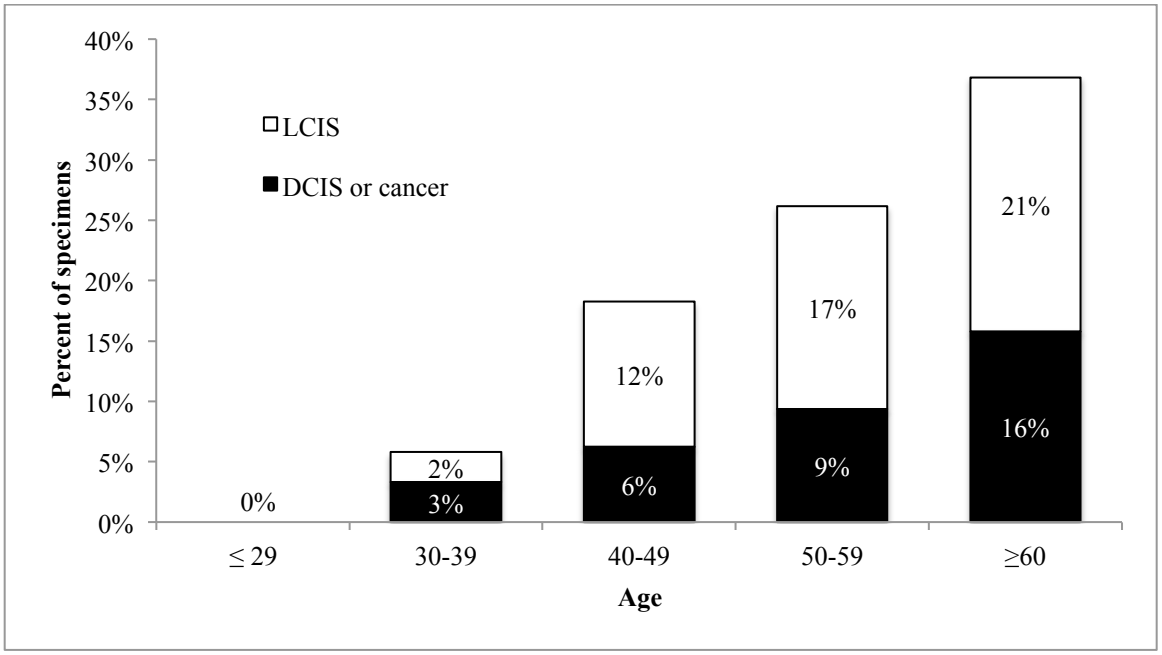
Simplified decision tree models



Two groups are considered in these models: patients with unilateral breast cancer considering CPM and BRCA positive patients considering BPM. The prior model starts from age 45 and the latter from age 40. At the starting point, patients choose either surveillance or PM. Those choosing undergoing PM undergo surgery within the first year and receive the appropriate post-operative follow-up. Patients opting for surveillance in either group undergo regular screening as recommended by the National Comprehensive Cancer Network guidelines. Every 5 year interval, a percentage of surveillance patients will remain cancer free and continue surveillance, whereas others will develop cancer and require therapeutic mastectomy with its appropriate follow-up. Costs were modeled using both implant and DIEP reconstruction for surveillance patients undergoing therapeutic mastectomy and patients opting for PM.

Figure 2

Percent of specimens with LCIS, DCIS, or cancer



As patients age, the overall rate of each specimen having LCIS, DCIS, or cancer increases gradually from 0% in patients under 29 to 36.8% in patients above 60 years of age.